

POINTS TO CONSIDER

SCIENTIFIC ABSTRACT

One of the major causes of morbidity and mortality in patients who receive bone marrow transplantation (BMT) from unrelated or mismatched donors is viral infection. This increased risk of infection relates to a number of factors including the immunosuppressive regimens these patients receive, delayed immune recovery and to the greater genetic disparity between donor and recipient resulting in defective interactions between antigen presenting cells and immune system effector cells. In most cases viral infection post BMT results from reactivation of latent virus and CMV, EBV and adenoviruses are the commonest viral pathogens causing disease after transplant.

In the absence of preventive measures, the incidence of CMV infection is 60-70% for patients at risk in the first 100 days after transplant. Approximately one third of these patients develop CMV pneumonitis, which is associated with very high mortality. The most frequently used drugs for prophylactic or preemptive antiviral therapy are Ganciclovir and Foscarnet. These drugs, in combination with IVIg, have been successful in reducing the mortality associated with CMV disease and in preventing early CMV disease¹. However, prophylaxis or preemptive treatment with Ganciclovir or Foscarnet has significant side effects and expense. In addition, prophylactic or preemptive therapy delays recovery of CMV specific CD4 and CD8 lymphocytes resulting in an added increased risk of developing persistent or late CMV disease². Further, with the increasing use of so-called submyeloablative or reduced intensity, highly immunosuppressive conditioning regimens, higher rates of CMV infections/reactivation have been observed due to prolonged immune suppression³. The onset of CMV disease/reactivation occurs later with these regimens and consequently delayed CMV disease has become a major problem⁴.

As viral complications in these patients are clearly associated with the lack of recovery of virus-specific cellular immune responses, reconstitution of the host with *in vitro* expanded CTLs is an effective approach to prevent and treat these diseases⁵. Adoptive immunotherapy with *in vitro* expanded CTLs has proved effective in preventing and treating diseases related to Epstein Barr virus (EBV) infections in hematopoietic stem cell transplant (HSCT) recipients⁶. A promising strategy to generate donor-derived CMV-specific CTL is the genetic modification of Dendritic Cells (DC) that direct the CTL response to virally transduced genes^{7, 8}. This approach allows expression of the whole protein leading to presentation of multiple, undefined antigen epitopes. Hence we plan to use a recombinant adenovirus encoding the CMV protein pp65 for transduction of donor-derived DC. These genetically modified DC will then be used as antigen presenting cells (APC) to generate CMV-specific CTL *in vitro*. For the expansion of the CMV-specific CTL, subsequent stimulations will use donor-derived Lymphoblastoid Cell Lines (LCL) transduced with the adenovirus-pp65 as the APC.

We propose to evaluate this approach for prophylaxis of CMV reactivation and disease in the recipients of matched unrelated donor or mismatched family member bone marrow allografts, who are at high risk for this complication. Initially, we will give the donor-derived CMV-specific CTLs to patients in a dose escalation study to determine their safety and immunologic and virologic efficacy.